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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/886,271	06/22/2001	Timothy G. Myers	41570	6793

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EXAMINER	
ROBINSON, HOPE A	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 10/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/886,271	MYERS ET AL.	
	Examiner	Art Unit	
	Hope A. Robinson	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 July 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-3,5-8,10-12 and 56-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-3,5-8,10-12,56-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 September 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's response to the Office Action mailed March 18, 2004 on July 19, 2004, is acknowledged.

2. Claims 4, 9 and 13-55 have been canceled. Claims 56-68 have been added. Claims 1-3, 6-8 and 11-12 have been amended. Claims 1-3, 5-8, 10-12 and 56-68 are pending and are under examination.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Specification

4. The specification is objected to because of the following informalities:

The specification is objected to because trademarks are disclosed throughout the instant specification and not all of them are capitalized or accompanied by the generic terminology. The use of the trademarks such as POROS®, for example, have been noted in this application (see page 34). It should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

The specification remains objected to as the Tables on pages 15-17 lists protein markers with Accession numbers (from SWISSPROT and NCBI, page 14 of the specification) and there is no disclosure of the specific sequences using the appropriate sequence identifier.

Correction of the above and compliance with the sequence rules is required.

Claim Objection

5. Claims 2-3, 11 and 68 are objected to because of the following informalities:

Claim 3 is objected to because the claim fails to further limit claim 2.

Claim 2, 11 and 68 are objected to because the claims recite a listing of protein markers exemplified in the tables on pages 15-17 of the instant specification, where Accession numbers (from SWISSPROT and NCBI, page 14 of the specification) are disclosed for each marker, indicating that the markers have a sequence which is not disclosed in the instant specification. The specific sequence for each marker needs to be provided in order to comply with the sequence rules.

Correction of the above and compliance with the sequence rules is required.

Claim Rejections - 35 USC § 112

6. Claims 1-3, 5-8, 10-12 and 56-68 are rejected under 35 U.S.C. 112, first paragraph, because the claimed invention is not enabled for the full scope of the claims. The specification on pages 15+ provides tables of markers for obesity, osteoporosis,

diabetes and osteoarthritis. However, the claims are directed to a method for determining a disease state for obesity, osteoporosis, diabetes and osteoarthritis (see for example claim 1) using protein markers (see for example claim 2) and a laundry list of markers are provided in a Markush listing (see for example claim 1). However, there is no indicia as to which marker corresponds to which disease. Does all four diseases have the same markers? The instant specification does not enable the scope of the claims. It is noted that the tables listed on pages 15+ indicate that the markers in claim 2, "19/HUSERFR3A"-UKN20/HUSERFRAC5" are markers for obesity, markers "36/HUSERFR3A-UKN6/HUSERFRAC5" are markers for Osteoporosis, markers "14HUSERFR3A-101/HUSERFRAC5" are markers for diabetes and marker "1992/HUSERFR6" is for osteoarthritis. Note that the instant claim language reads on all protein markers for all four diseases, instead of specific markers for specific diseases. Thus, the selection of marker "19/HUSERFR3A cannot be used to determine the disease state of osteoporosis, diabetes and osteoarthritis, but the claim does not make this distinction, which is not supported by the instant specification.

In addition, there is no relationship between obesity, osteoporosis, diabetes and osteoarthritis to demonstrate the same marker can be used. As such the method is non-specific as the diseases as claimed are treated as being the same, there is no indicia as to the levels of the sample versus the control for the individual disease or the relationship between each disease to be able to use the same marker. The instant specification provides tables on pages 15-17 of four diseases recited in the claims and disclose markers, which do not overlap for each disease, thus demonstrating that a marker is specific to a disease. The specification does not describe/provide examples to demonstrate that the markers identified in the claims/tables are applicable for all the diseases set fort in claim 1 for example. Note that claim 1 reads on all possible

markers, which is not supported by the instant specification. It is noted that claim 2 limits the scope of claim 1, however, independent claim 1 needs to stand on its own and claim 2 does not distinguish which marker is associated with what disease. Furthermore, the breath of claim 1 for example encompasses non-genetic and genetic variations, which is not enabled by the instant specification, which only discloses non-genetic markers. For example, on page 5 of the specification it is disclosed that "the invention determined non-genetic markers by searching for proteins present in abnormal abundances between monozygotic twins where the twins are discordant for the disease state".

Additionally, the method as set forth in claim 1 provides the steps of: (a) obtaining a biological sample containing protein, (b) measuring levels of protein markers of the disease state and (c) comparing the levels of said markers to a standard. These steps alone cannot achieve the claimed objective in the preamble. On page 5 of the instant specification it is stated that "initially all readily detectable proteins are measured, but after the markers are determined, an assay for the markers alone is sufficient. Clearly the method is missing essential steps between the obtaining a sample and measuring levels of protein markers such as an identification step for the markers. Thus, one of skill in the art would have to engage in undue experimentation to determine what disease correspond to what marker in for example claim 1 and for claim 2 determine which marker correspond to which disease and determine if any marker can be used for all four disease. Due to the large quantity of experimentation necessary to generate the protein markers for the diseases recited in for example claim 1 and to match the appropriate marker with the appropriate disease in claim 2 and due to the lack of adequate guidance/direction provided in the instant specification, this is merely an invitation to the artisan to use the current invention as a starting point for further experimentation.

Note also the claim 1 as amended recites a method for determining a disease state of obesity, osteoporosis, diabetes or osteoarthritis in a subject...obtaining a biological sample containing protein...measuring levels of protein markers..., however, there is no indicia as to what information is to be gleaned from the measurement of the levels. It is noted that claim 5 recites that the levels of protein markers determines the relative severity of the disease state, however, the level of marker "19/HUSERFR3A" will not determine the relative severity of the disease state for example diabetes. Thus, the method as claimed cannot accomplish the claimed objective. Further, in view of the uncertainty of whether the right marker will be associated with the right disease, the use of the term relative severity enhances the unpredictability of the method as claimed as "relative" is a latent term. Note also that claim 12 although no longer dependent on claim 11, is still written in dependent form with the limitation of hypertension and if applicant intends for this claim to depend from claim 1, claim 1 does not provide support for that disease. Essentially, a skilled artisan would not be able to obtain the protein marker of claim 12 as the claim lacks adequate guidance/direction.

Note also that claim 60 is directed to a method of determining hypertension in a human subject using protein markers and the claim does not identify the specific markers. It is noted that claim 61 provides the missing information in claim 60, however, claim 60 needs to stand on its own and reads on any marker including those described in the Tables on pages 15+ for other diseases.

The specification does not provide clear guidance as to the proteome of the claimed invention to allow one of skill in the art to practice the claimed invention commensurate in scope with the claims. For example , claim 6 recites "measuring levels of individual proteins in a proteome" and the specification on page 5 refers to the proteome as a signature or proteomic pattern created by protein markers (see also

claim 63). It is also disclosed that the proteome is a large number of proteins expressed in a biological sample, representing the total, relevant portion or preferably all detectable proteins by a particular technique or combination of techniques. Clearly, the description provided is inconsistent and confusing, whereas, the prior art states that "the image of the displayed proteins obtained is the proteome" (see Page et al., Research Focus, vol. 4, no. 2, February 1999). Additional, the tables listed on pages 15-17 (and recited in for example, claim 2) provides a listing of protein markers labeled with Accession numbers, however, the specification does not provide adequate guidance as to the source of the accession numbers to make the information readily accessible and to be enabling. Therefore, one of skill in that art would have to engage in significant experimentation to practice the claimed invention in a manner that reasonable correlate with the invention as claimed.

Further, note that claim 56 is directed to a sample that is a body fluid which contain the protein markers, the breath of the claim encompasses any body fluid such as urine, saliva, blood plasma, hydroplasma, tears, sweat, mucus, serum etc., and the instant specification does not demonstrate the use of any bodily fluid in the instant method, see for example page 10 where it is disclosed that the biological sample may be taken from blood, plasma, serum or urine.

In view of the foregoing, one of skill in the art would require guidance, beyond that provided in the instant specification, in order to practice the claimed invention commensurate in scope with the claims. See *In re Wands* for further details such as the factors used herein for determining enablement.

Response to Applicant's Arguments:

7. The response on page 15 state that the claims have been amended, however, the amendments to the claims prompted the institution of another rejection under 35 U.S.C. 112, first paragraph for the reasons stated above. Applicant state that "proteome" as defined by the specification is not confusing and the term is not mentioned on page 5 of the specification, however, see lines 14-17 of page 5 where proteomic patterns are discussed. As the claim was not amended and new claim 63 is also directed that subject matter the issue at hand remains. Applicant further state that the accession numbers recited in the instant specification are identified as coming from SWISSPROT and NCBI, page 14 of the specification, however, the discrete sequences for each protein marker needs to be disclosed, applicant is directed to the sequence rules. Therefore, the rejections of record remains and new rejections have been instituted based on amendments made to the claims.

8. Claims 1-3, 5-8, 10-12 and 56-68 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 and the dependent claims hereto are indefinite for the recitation of "a biological sample containing protein from said subject", because the term "protein" is confusing as it is not clear which protein is being referred to; said biological sample contains thousands of proteins. The skilled artisan would not know which particular protein to manipulate (see also claim 60 and the dependent claims hereto). The dependent claims are also included in this rejection.

Claim 6 is confusing for the recitation of "levels of individual proteins in a proteome", as a particular protein in a particular proteome of a particular biological

sample can only have one level. How can multiple levels be determined and compared? See also page 5 of the specification where it is stated that "proteome" is equivalent to a "signature". The dependent claims hereto are also included. See also claim 63.

Claim 12 is indefinite because the claim is a dependent claim, however, no dependency is provided, thus is incomplete, see where the claim recites "a protein marker of?" If the claim is to depend from claim 1, note that it would lack antecedent basis as claim 1 does not recite "hypertension" (see also claim 68). The claim is also confusing for the recitation of the phrase "...said protein marker in a sample from a subject with the disease state differs from the level of said protein..." (see lines 4-5 of the claim). The dependent claims hereto are also included.

Response to Applicant's Arguments:

9. The response on page 16 state that the generic use of "protein" is not indefinite as "a cup of milk contains 8 grams of protein (the class of polypeptide compounds generally made up of any number of individual protein molecules)". This argument is not persuasive and the issue raised remains. It is suggested that the claim is amended to recite "a protein".

As the rejection over claim 2 is withdrawn applicant's arguments will not be addressed.

Applicant state that claim 6 has been amended to clarify the claim, however, the rejection of record remains as the amendments made and the applicant's response did not address all the issues raised.

Note that the rejection over claims 8 and 11 have been withdrawn and a new rejection has been instituted over claim 12 based on amendments made for the reasons stated above.

Note the new grounds of rejections over the newly submitted claims.

This response is deemed sufficient to address the issues raised by applicant.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 60 and 62-67 are rejected under 35 U.S.C 102(b) as being anticipated by Pleibner et al. (Electrophoresis, vol. 19, pages 2043-2050,1998).

Pleibner et al. teach a method that uses protein markers to identify alterations of the cardiac protein pattern in renovascular hypertension, which provides useful information regarding the disease state. As the presence of the disease is determined during the process to determine the disease state claim 60 is anticipated. For instance, the method of Pleibner et al. detected a protein that is likely to be in the same pathway of the disease stage, for example, early stage of hypertension (claim 62, see page 2049 of the reference). Pleibner et al. used a group of hypertensive (claims 63) and control rats and compared the patterns by computer assisted two-dimensional (2-D) gel

electrophoresis (claims 66-67) and analysis including univariate and multivariate statistical approaches (claims 64-65, see pages 2043-2044), thus a p value of 0.01 or 0.001 can be achieved. Total proteins, for example, proteome of tissue samples are separated and the level of individual protein separated is measured through 2-D gel analysis assisted with computer analysis (claim 66, see page 2044, left column). Thus, the limitations of the claims are met by this reference.

Response to Applicant's Arguments:

11. Applicant's comments regarding the art rejection of record is noted. The rejection has been withdrawn, however, the reference is applicable over newly submitted claims 60 and 62-67 for the reasons stated above.

Conclusion

12. No claims are presently allowable.

13. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hope A. Robinson whose telephone number is 571-272-0957. The examiner can normally be reached on Monday-Friday.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber, can be reached at (571) 272-0925.

The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Hope Robinson, MS ~~HR~~ 9/30/04

Patent Examiner

JON WEBER
SUPERVISORY PATENT EXAMINER